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Lupus: The Wolf That Ravages The Immune System

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The Wolf That Ravages

The Immune System

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LUPUS: The Wolf That Ravages

The Immune System

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Fatigue absorbed her whole body, both physically and emotionally. There was pain in her legs below her knees, and they felt as though they were filled with cement. Her feet were always inflamed and aching. Her fingers were tender and a colorful red or blue. She was losing her hair by the handfuls. There were nodules on her elbows and fingers (Aladjem 145). She had problems with her eyes, and her "throat hurt all the time" (Aladjem 146). These numerous problems were consuming the life of Henrietta Aladjem, yet no doctor knew what, if anything, was wrong with her. They simply led her to believe that it was all in her head.

Henrietta Aladjem was finally diagnosed with lupus after several months. By this time her kidneys were severely damaged. Furthermore, there was no known cure for lupus. In 1958, her lupus went into remission and stayed in remission for more than thirty-two years. No one knew why she went into remission, or why it has lasted so long. She has not forgotten her battle with this vicious disease, however. Aladjem has written books about lupus and works

with the Lupus Foundation of America in hopes of teaching others about this mysterious disease (Aladjem 153).

As one can tell from Aladjem's description, lupus is a devastating disease. Even its name, which means wolf in Latin, suggests the fierceness of this disease. Lupus, which is short for systemic lupus erythematosus (SLE), is not rare (Hales 60). "It is more prevalent than muscular dystrophy, multiple sclerosis, cystic fibrosis, rheumatic fever, pernicious anemia, Hodgkin's disease, or leukemia," yet it is virtually unknown to the general population (Aladjem 8). Lupus has been diagnosed in approximately 500,000 Americans. Ninety percent of those diagnosed with lupus are women. It has been estimated that lupus affects half a million more people, but they do not know what is wrong (Hales 60). In addition, SLE affects black women three times more often than white women (Aladjem 4). Most of the women are in their childbearing years with an average age of twenty-nine (Blau and Schultz 31).

Most lupus patients have only mild, or possibly moderate, symptoms of this disease. Yet, 10% have the life-changing, and potentially life-threatening, SLE that Henrietta Aladjem described (Hales 60). One might ask, what exactly is lupus? And, what would be capable of causing a disease to be so variable in each individual it strikes? Obviously, SLE is a multisystem disease that can affect everything from the skin to the heart and lungs (McCarty, Valencia, and Fritzler 8). It is also a collagen-vascular disease, which implies the involvement of connective tissue and blood vessels (Aladjem 9). In addition, it is an inflammatory autoimmune disorder, which means that the body attacks its own tissues (Hales 60). Although researchers have classified lupus in several ways, they have not been able to find the exact cause of this disease.

SYMPTOMS

Perhaps the best way to understand the complexity of lupus is to look at how it manifests itself in the body.

Essentially, what symptoms might a twenty-five year old black female show if she has systemic lupus erythematosus? "SLE can affect any part of the body" (Aladjem xvi). However, most patients experience only a few of the many symptoms associated with SLE. Some of the patient's symptoms may be rashes, joint pain, fever, weight loss, fatigue, anemia, heart problems, kidney and sensory malfunction, false-positive tests for syphilis, sensitivity to the sun, pleurisy and pneumonia, hair loss, mental or emotional problems, nausea, vomiting, and jaundice (Blau and Schultz 10). Other symptoms include Raynaud's phenomenon (the toes or fingers turn blue or white), mouth ulcers, muscle pain, lung problems, and liver enlargement (Aladjem xvii-xviii). Again, one must remember that each SLE patient is different and that the disease will affect that person in its own way. It has been noted, however, that some symptoms are commonly recognized before others. The first symptoms usually include "mild, but

persistent aching in the joints," rashes, a low, persistent fever, fatigue, weight loss, loss of appetite, swollen lymph nodes, and sensitivity to the sun (Blau and Schultz 11-12). In addition to knowing the symptoms of SLE, researchers also know the frequency with which they occur in SLE patients. The symptoms and their frequencies are as follows:

Arthralgia (achy joints)	95%
Fever over 100°F (38°C)	90%
Arthritis (swollen joints)	90%
Skin rashes	74%
Anemia	71%
Kidney involvement	50%
Pleurisy	45%
Butterfly rash	42%
Photosensitivity	30%
Hair loss	27%
Raynaud's phenomenon	17%

Seizures	15%
Mouth ulcers	12%

(Aladjem xvi).

CRITERIA FOR SLE

Because of the many symptoms listed above, systemic lupus erythematosus is a very difficult disease to diagnose. It often manifests itself in so many ways that one case of SLE appears virtually unrelated to another case. In 1970, the American Rheumatism Association developed its first set of criteria for SLE. There were fourteen categories with a total of twenty-one manifestations. In order to be diagnosed with SLE, patients had to exhibit at least four of the fourteen items. The problem with this standard was that only 67% of one doctor's SLE patients actually had four manifestations at the time a diagnosis was needed, but 94% of the patients eventually met the criteria over a period of time (Wallace and Dubois 17). This lack of ability to diagnose patients at the time they were having a few symptoms, along with other

problems with the 1970 criteria, led to the development of a revised list of criteria that was published in 1982. The criteria are as follows:

(1) Malar, or butterfly, rash. This rash is located on the nose and cheeks. It may be flat or raised.

(2) Discoid rash. This is expressed as "reddish raised patches" on the body. The patches are "disc-shaped, thick, and scaly" (Blau 18).

(3) Photosensitivity. An unusual reaction to the sun results in a skin rash.

(4) Oral ulcers. These are ulcers in the throat or mouth that are usually painless.

(5) Arthritis. This involves more than one peripheral joint, including those of the lower jaw, shoulders, arms, hands, hips, feet, and legs. The arthritisis characterized by tenderness, swelling, and pain upon use of the joint.

(6) Serositis.

(a) Pleuritis. The pleura, which is "the membrane lining of the chest," is inflamed (Blau and Schultz 19). Or,

(b) Pericarditis. The pericardium, which is "the outer membrane surrounding the heart," is inflamed (Blau and Schultz 19).

(7) Renal disorder.

(a) Proteinuria. The levels of certain proteins in the urine are increased. Or,

(b) Cellular Casts. These cellular casts are "fragments of elements normally found in the blood" (Blau and Schultz 19). The elements may be "red cell, hemoglobin, granular, tubular, or mixed" (Wallace and Dubois 18; McCarty, Valencia, and Fritzler 8). They suggest the presence of blood in the kidney.

(8) Neurologic disorder.

(a) Seizures. Or,

(b) Psychosis.

(9) Hematologic disorder. This is a result of a shortage of different types of blood cells.

(a) Hemolytic anemia. This results from "too rapid destruction of red blood cells" (Blau and Schultz 19). Or,

(b) Leukopenia. This is a lack of platelets. Or,

(c) Lymphopenia. This results from a lack of white blood cells. Or,

(d) Thrombocytopenia. This is a deficit in thrombocytes.

(10) Immunologic disorder.

(a) Positive LE cell test. This is the lupus erythematosus cell test. When it is positive, "white blood cells that have ingested nuclei from damaged cells" are present (Aladjem xxi). Or,

(b) Anti-DNA. The antibody to native DNA is present in an abnormal titer. Or,

(c) Anti-Sm. The antibody to the Smith antigen is present. Or,

(d) False-positive syphilis test.

(11) Antinuclear antibodies. These antibodies can be detected by an assay such as immunofluorescence.

As with the 1970 criteria, a person is considered to have systemic lupus erythematosus if they meet four of the eleven criteria at the same time or during different times of observation. The above list of criteria have been compiled from Aladjem (xx-xxi); Blau and Schultz (18-19); McCarty, Valencia, and Fritzler (8-9); Schur (6-7); and Wallace and Dubois (18).

THE IMMUNE SYSTEM

Systemic lupus erythematosus "is an example of the immune system gone awry" (Aladjem 21). The immune

system is the body's defense against foreign invaders. The goal of this system is to distinguish between its own substances and foreign substances (Stryer 889). The immune response to nonself antigens involves one of two different strategies. One strategy is the humoral immune response. In this response, antibodies against the foreign antigen are synthesized by B lymphocytes. The antibodies bind the antigens, and the complex is either precipitated or identified for destruction by macrophages (Mathews and van Holde 248). The other strategy, the cellular immune response, involves T lymphocytes, which kill foreign cells. The T lymphocytes are also involved in the humoral response because they assist the B lymphocytes in functioning (Stryer 889). By looking at the two normal immune responses and their components in detail, one can better understand the immune system, and thus, the effects of lupus on it.

Lymphocytes

The humoral immune response centers on the proper

functioning of lymphocytes, a specialized group of white blood cells (Blau and Schultz 62). Using monoclonal antibodies, lymphocytes have been divided into two groups: antigen specific cells and antigen nonspecific cells. T cells and B cells, which make up 85% of the total blood lymphocytes, fall into the antigen specific category (Wallace and Dubois 195).

The T cells have a receptor that is made of "a two chain heterodimer with an antigen binding variable region homologous to the B cell immunoglobulin receptor" (Wallace and Dubois 195). The antigen that is associated with the antigen binding region is called the T3 surface antigen and is found on all mature T cells. The T3+ cells are classified according to which monoclonal antibody they react with. Those that react with T4 monoclonal antibodies are inducer/helper cells, and the ones that react with T8 monoclonal antibodies are cytotoxic/suppressor cells. Using other monoclonal antibodies, the T4+ lymphocytes can be

further classified as suppressor inducer cells or helper cells (Wallace and Dubois 195).

As with most classification systems, however, there are exceptions to the rules. Even though the T4+ cells are classified as inducer/helper cells, there are certain T4+ cells that recognize and kill cells which have "foreign Class II (DR) markers," and other T4+ cells that possess suppressive abilities. Some T8+ cells are exceptions to the rules, also. Recall that T cells fall into the antigen specific category. Typically, T8+ cells stain very brightly when they react with the T8 monoclonal antibody. These are classified as antigen specific cells because they recognize and react with "Class I histocompatibility determinants." Some T8+ cells, however, stain dimly and represent a separate population that is not activated by the class I markers. These dim T8+ cells are classified as antigen nonspecific cells because they can be stimulated by lymphokines directly (Wallace and Dubois 195).

Like the majority of T cells, B lymphocytes are classified as antigen specific. These cells are believed to be derived from the bone marrow (Sheeler and Bianchi 648). B lymphocytes display two classes of immunoglobulin receptors: IgM and IgD. They have other specific surface markers that can be detected by monoclonal antibodies B1 and Leu 12 (Wallace and Dubois 195).

Lymphocytes that do not have B cell markers or react with T3 antigen are antigen nonspecific cells. They are also known as null cells. Throughout the 1970's, it was thought that null cells did not have the CD2 receptor, also known as the receptor for sheep erythrocytes. Now, it is known that monoclonal antibodies which detect the CD2 receptor react with the null cells. This is important because the presence of the CD2 receptor was once a specification for the T cells. Another type of receptor, the CR3 receptor, is found on all null cells. This receptor reacts with the iC3b complement component (Wallace and Dubois 195-196).

There are two principal groups of null cells: L cells and other. The L cells "display high density Fc receptors for IgG, mediate natural killer and antibody-dependent cytotoxic activity, and suppress antibody production." The "other" null cells do not have the Fc receptors, but do have the CR3 receptors. They suppress the production of antibodies and amplify the proliferation of antibodies (Wallace and Dubois 196).

To be able to fully comprehend the complexity of the overall immune response, one must understand that every lymphocyte cannot function completely on its own. For instance, the T4+ inducer/helper cells cannot recognize foreign antigens by themselves. In order for these lymphocytes to recognize an antigen, the antigen must be in combination with self HLA DR, which are the gene products of the Class II major histocompatibility complex (MHC). The intensity and quality of the immune response is determined by the self DR molecules. The primary function of the HLA

DR is to stimulate helper cells that promote production of antibodies, or to stimulate suppressor cells that produce a state of tolerance or nonresponsiveness. These lymphocyte responses are "MHC-restricted immune responses" because they require self-recognition (Wallace and Dubois 197).

T8+ lymphocytes, like the T4+ cells, are self-reactive. These T8+ cells can be sensitized to a virus. In order for the sensitized lymphocytes to then kill the virally infected cell, the viral antigen must be in combination with "self Class I MHC gene products." In other words, both the antigen and the MHC markers must be together to be recognized by the T8+ cells (Wallace and Dubois 197).

Humoral Immune Response

In the past, it was believed that B cells that had the potential to make autoantibodies were removed from the immune system at birth. Now, it is known that B cells capable of making autoantibodies such as anti-DNA are present in the blood of healthy individuals (Wallace and

Dubois 197). B cells, however, are not activated solely by antigen. The antigen must be in combination with T helper cells in order to activate B cells (Aladjem 22). Therefore, autoantibodies are usually not present in the blood because of the lack of T cell help or because of active suppression (Wallace and Dubois 198).

These B cells and T cells are central to the humoral immune response to foreign antigens. The humoral immune response occurs according to the clonal selection theory, which explained many of the problems in conceptualizing the immune response when it was developed. Some of the ideas that were explained are as follows. Production of antibodies rises exponentially when an antigen is present because of a tremendous increase in the amount of antibody-producing cells. Secondly, when an antigen appears for the second time, the response is much greater and much stronger because more cells against that antigen are already present. In addition, the "deletion of an entire clone of cells" results

in immunological tolerance to that particular antigen (Ada and Nossal 66). The immune response, according to the clonal selection theory, can be divided into 3 steps: (1) Antigen presentation, (2) T-cell activation, and (3) B-cell maturation (Wallace and Dubois 197).

In the first step, the antigen is recognized by T inducer cells. Recall that in order for the T inducer cell to be activated, the antigen must be in combination with self DR molecules, which are presented by a macrophage. Upon interaction of these cell types, two growth factors are secreted. One growth factor is interleukin 1 (IL-1), which is secreted by the macrophage and influences both T-cell and B-cell differentiation. The other growth factor, secreted by T cells, is interleukin 2 (IL-2). It is responsible for "activation and clonal expansion of T cells" (Wallace and Dubois 198).

The second step "is the activation and proliferation of other resting T cells responsive to antigen." Because resting T helper cells do not have receptors for interleukin 2, they

cannot bind that particular lymphokine. After antigen-presenting cells activate the T helper cells, IL-2 receptors develop. The T helper cells are then able to undergo clonal expansion and secrete B cell helper factors, known as "T-cell replacing factors" (Wallace and Dubois 198).

In the final step, B cells are activated and matured to antibody-secreting cells (Wallace and Dubois 198). B lymphocytes are derived from B stem cells that are located in the bone marrow. Each B lymphocyte produces an immunoglobulin molecule that has a binding site capable of recognizing specific shapes. These immunoglobulins, or antibodies, are located on the outer surface of the B lymphocyte. When an antigen binds to one of these antibodies, the B lymphocyte is stimulated to replicate and produce plasma cell clones (Mathews and van Holde 250). This process is aided by the previously mentioned T-cell replacing factors that are derived from the T helper cells. The first T-cell replacing factor is B-cell growth factor

(BCGF), which is a lymphokine that combines with antigen to induce B-cell proliferation. The second T-cell replacing factor is B-cell differentiation factor (BCDF). It is a lymphokine that "stimulates activated B cells to synthesize antibody." Neither of these lymphokines are MHC-restricted; thus, they can act on any B cell. The most important thing to remember is that binding of a ligand to the B cell antigen receptors and the presence of T-cell replacing factors are necessary for a B cell to become immunoglobulin-secreting cells (Wallace and Dubois 198).

Once the third step is completed, the antibodies that were secreted by the plasma cells can rid the body of the foreign antigens in several different ways. First, the immunoglobulins may interact with soluble, or free, antigens and cause precipitation of the antigen-antibody complex. Secondly, the antibodies and the surface antigens of the foreign particle may interact and cause agglutination. Macrophages then rid the body of these complexes by

phagocytosis. Finally, the antibodies may promote complement fixation, which involves a cascade of reactions following the binding of complement proteins to antigen-antibody complexes (Sheeler and Bianchi 657-659).

Cellular Immune Response

Both the humoral and the cellular immune responses are involved in the defense of the body, but they have different functions. The role of the humoral immune response is to "combat bacteria and viruses in extracellular media." The cellular immune response, however, "destroys virus-infected cells, parasites, and cancer cells" (Stryer 911).

In addition to having a different function than the humoral immune response, the cellular immune response also has a very different mechanism for killing the foreign invaders. Cytotoxic, or killer, T cells play the central role in the cellular immune response. Unlike the soluble antibodies of the humoral response, the T cells carry their own receptor molecules on their surface. T cells, like antibodies, have

many different binding specificities (Mathews and van Holde 254). However, unlike antibodies, they only recognize short peptides sequences (less than 10 residues). "In essence, antibodies recognize native macromolecules, whereas T cell receptors recognize fragments derived from them" (Stryer 912). These fragments must be bound to proteins of the major histocompatibility complex in order to be recognized by the T cell receptor. Once an appropriate antigen-MHC protein complex is identified by a killer T cell, the T cell releases perforin. Perforin is a protein that causes the formation of pores in the foreign cell's plasma membrane. Basically, these pores kill the cell by allowing the critical components of the cell to diffuse out (Mathews and van Holde 254).

An example of the cellular immune response can be seen in the way that the body responds to viral infection. When a virus attacks a cell, the virus breaks down into two components--the nucleic acid, which enters the host cell, and

the proteins in the viral coat, which stay at the surface of the cell. Because the infected cell now has both viral antigens and Class I MHC markers, it can be recognized by the cytotoxic T cells. The cytotoxic T cells then attach themselves to the infected cell and kill it before the virus has a chance to replicate. This is done by the transfer of cytotoxins into the infected cell. One cytotoxic T cell is capable of killing several host cells (Sheeler and Bianchi 662).

ABNORMAL IMMUNE RESPONSE IN SLE

As previously described, the immune system normally works together in a very precise manner to protect the body from foreign antigens that can cause infection, inflammation, and other problems. In systemic lupus erythematosus, however, this delicate balance is upset, and the body no longer functions in its orderly way. Through looking at the various effects of SLE on the immune system, one can better understand the disease itself and the necessity of a properly working immune system.

Abnormal Lymphocyte Amounts

Lymphocytes play the central role in both the humoral and the cellular immune responses. Therefore, changes in the overall numbers and/or in the percentages of the lymphocytes should have noticeable effects on the immune response. This is precisely what appears to happen. Overall, T cell, B cell, and null cell numbers are usually decreased in patients with active SLE. All subsets of the lymphocytes have decreased absolute counts because of lymphopenia. The relative percentages of each subset, however, may be decreased, normal, or increased. The total percentage of T cells is usually normal. T3+ lymphocyte percentages are often decreased, especially in patients receiving prednisone for treatment. T8+ lymphocytes (cytotoxic/suppressor cells) have normal or increased percentages, while T4+ lymphocytes (inducer/helper cells) have decreased percentages. This results in a T4+ to T8+ ratio that is abnormally low. The percentage of B cells in SLE is normal

or decreased. The percentage of antigen nonspecific lymphocytes (null cells) is decreased. In addition, the proportions of the two major subsets of null cells (L cells and other) are reversed. The percentage of L cells is greatly decreased (Wallace and Dubois 200), while the "other" category is increased (Wallace and Dubois 196). There is evidence that "a strong relationship exists between high titers of antilymphocyte antibodies, disease activity, and the lymphopenia of SLE" (Wallace and Dubois 200).

Abnormal B Lymphocyte Function

Many researchers have found that the B cells of SLE patients are hyperactive (Aladjem 28). Wallace and Dubois discuss the presence of B cell hyperactivity and the specific functions of the B lymphocytes that are increased (200). These hyperactive functions are as follows: reactions between antibodies and certain viral antigens, immunoglobulin turnover rates, and blood mononuclear cells that proliferate spontaneously (thousandfold increase). In

addition, "lymphocytes in B cell-enriched fractions" proliferate spontaneously in patients that have active SLE and in those with inactive SLE (Wallace and Dubois 200).

B cell hyperactivity is not an isolated occurrence, however. It is observed along with T cell activation. There is a known correlation between immunoglobulin-secreting cells and "endogenously activated T cells." SLE patients show an increase in the number of activated B cells and an increase in the number of B cell precursors in the bone marrow and in the peripheral blood, as well as the increase in activated T cells (Wallace and Dubois 201).

Although there is an increase in spontaneous activity, B cells secrete immunoglobulin in unusually low amounts in response to the pokeweed mitogen (PWM). This occurs in both active and inactive SLE. Different theories about the lack of reactivity to pokeweed mitogen exist. Because PWM is T cell dependent, one possible theory is that increased suppression or decreased helper activity by lymphocytes

could cause the lowered reactivity. Another possible theory deals with the activation of B cells. In patients with active SLE, B cells may be spontaneously activated. Once the B cells are activated, they should not be expected to respond to pokeweed mitogen. However, patients with inactive SLE may have an impaired response to pokeweed mitogen also. Because they have low levels of spontaneous B cell activation, this above explanation is invalid (Wallace and Dubois 201).

The lack of B cell response to pokeweed mitogen can be corrected by providing B cell growth factors or helper cells. By adding autologous T4+ lymphocytes, immunoglobulin production by SLE B cells can be increased to normal. Therefore, it appears that "the decreased percentages of T4+ inducer/helper cells along with proportionately increased suppressor lymphocyte subsets...contribute to defective B cell responsiveness in SLE." In addition to the pokeweed mitogen studies, the production of antigen specific

antibodies has been studied. The results confirm that SLE B cells are hyporesponsive and that the hyporesponsiveness is caused by a T helper cell defect (Wallace and Dubois 201).

Abnormal T Lymphocyte Function

The abnormal behavior of T lymphocytes described above interferes with their ability to interact with other cells. It has been shown that when normal T lymphocytes are combined with SLE serum, normal T suppressor cells cannot develop (Aladjem 28). Furthermore, the proliferation of disease lymphocytes and normal lymphocytes is inhibited. The IgG fractions in these sera were inhibited as well. Studies have also shown that the proliferation of lymphocytes upon contact with soluble antigens is decreased in SLE. Additionally, the responsiveness of T lymphocytes to allogenic lymphocytes and in the "autologous mixed lymphocyte culture (AMLR)" is decreased. Normally, in the AMLR, major histocompatibility complex markers on non-T cells are recognized by T4+ lymphocytes. Interleukin 2 is

secreted, and T4+ and T8+ cells proliferate. However, because SLE T4+ cells cannot produce interleukin 2, the AMLR is decreased in SLE (Wallace and Dubois 202).

In essence, the decrease in SLE lymphocyte proliferation is caused by one or more of three factors. The proportion of cultured lymphocytes may be relatively decreased; suppressor monocytes may be present; or factors capable of inhibiting proliferation may exist (Wallace and Dubois 203). Furthermore, decreased interleukin 1 and interleukin 2 production contributes to the decrease in lymphocyte proliferation (Aladjem 28). By adding normal helper cells, interleukin 1, or interleukin 2, these T cell defects can be corrected in SLE patients (Wallace and Dubois 203).

In addition to the defects in T lymphocyte proliferation, there are defects in the T helper cell activity. Activity induced by mitogenic lectins is decreased or normal. Immunoglobulin synthesis induced by pokeweed mitogen shows both decreased and normal helper activity. Helper

activity induced by specific antigens is decreased. In one study, SLE B cells were cocultured with normal T cells. The SLE B cells responded to the normal T cells. Conversely, however, the T cells of SLE patients were unable to help normal B cells. B cell colony formation, which is supported by the T cells, is defective in SLE patients also (Wallace and Dubois 205). Therefore, it can be concluded that T helper cell activity in SLE is abnormal regardless of the effect of the disease on the B lymphocytes.

The T suppressor cell activity of T8+ cells is also defective in SLE patients. Normally, T cell proliferation, antibody production by B cells, and the generation of cytotoxic effector cells can be suppressed by lymphocytes activated by concanavalin A. In SLE, this suppressor activity is decreased. It has been reported that SLE patients do not have a particular population of short-lived lymphocytes that are known to circulate in the blood and to have the ability to suppress the lymphocyte proliferation. In addition to this

lack of suppressive lymphocytes, there is evidence for the inadequate activation of suppressor cells. This evidence includes a decrease in T4+ cells (inducer/helper cells), a decrease in interleukin 2 production, and "antilymphocyte antibodies cytolytic for T4+ suppressor inducer cells as well as T8+ suppressor effector cells." Reports have shown that proper suppressor signals can overcome this regulatory defect. Therefore, decreased suppressor activity can result not only from a lack of suppressor cells but also from inadequate induction. Furthermore, inadequate suppression can be caused by the increased number of T8+ lymphocytes that inhibit interleukin 2 production (Wallace and Dubois 206).

In addition to the numerous other problems with T lymphocytes, SLE patients have decreased "antibody-dependent cellular cytotoxicity (ADCC)" that correlates with disease activity. In other words, certain lymphocytes that have Fc receptors for IgG possess the ability to kill cells

coated with IgG. The sera of SLE patients contain IgG lymphocyte antibodies or immune complexes that can block ADCC. However, these IgG antibodies are also capable of inducing ADCC against T lymphocytes. In studies, "normal T cells sensitized with SLE serum became target cells in ADCC." This may help to explain the lymphopenia of SLE (Wallace and Dubois 206).

Abnormal Natural Killer Cells

Natural killer cells, or NK cells, are responsible for injecting cytotoxins into virus-infected cells during the immune response. When the NK cell and the infected cell interact, interferon is produced in great amounts. It is responsible for the rapid proliferation of the natural killer cells (Sheeler and Bianchi 669). Like the B cells and the T cells of an SLE patient, the natural killer cells act abnormally. Their activity is decreased (Aladjem 30). It has not yet been established whether or not this decrease in activity correlates with the presence of active disease. A few possible

explanations for the natural killer cell defect exist. The NK cell may have an intrinsic defect; there may be inhibition of NK cell activity by corticosteroid treatment; or the SLE serum may contain antilymphocyte antibodies. The last possibility seems to be the most probable because "antilymphocyte antibodies specific for NK cells have been described" (Wallace and Dubois 206).

Two lymphokines, interferon and interleukin 2, play important roles in NK cell activity. In normal controls, interferon and interleukin 2 greatly enhance NK cell activity. Interleukin 2 can stimulate Leu 11+ cells to secrete gamma interferon. The effect of interferon on natural killer cell activity in SLE patients has been variable in studies. Interferon did not enhance low NK cell activity in SLE patients, but it did augment the activity of patients that already had high natural killer cell activity. In another study, interferon only had a modest effect on NK cell activity, while interleukin 2 augmented the cytotoxicity of natural killer cells

to normal levels (Wallace and Dubois 206).

Overall, it appears that natural killer cell activity in SLE patients is abnormal because of a significant decrease in the number of NK cells, the presence of antilymphocyte antibodies capable of blocking cytotoxicity, and a decreased response to lymphokines (Wallace and Dubois 207).

Abnormal Monocytes

Normally, monocytes have a regulatory role in various aspects of the immune response. They help regulate the proliferation of lymphocytes, the production of lymphokines, and the activation and maturation of T cells and B cells. SLE monocytes, however, behaved abnormally in several experiments. They inhibited pokeweed mitogen-induced immunoglobulin production. When the monocytes were removed, immunoglobulin production increased. Monocytes blocked the B cell response to "Staphylococcus aureus Cowan I antigen," also. This can be explained as follows. Immunoglobulin synthesis by B cells can be enhanced by

interleukin 1. Although the monocytes are capable of producing IL-1, the production of IL-1 inhibitors can be stimulated by immune complexes, which are often present in the blood of SLE patients. In addition, decreased interleukin 1 production has been reported in SLE. Studies have shown that the addition of interleukin 1 and interleukin 2 allows lymphocyte function to overcome the suppressive effects of abnormal SLE monocytes (Wallace and Dubois 207).

Normal and Abnormal Lymphokines

Lymphokines, or interleukins, are secreted by certain T helper cells and are responsible for activating macrophages and other lymphocytes. The goal of lymphokine secretion is to accumulate macrophages and lymphocytes in an infected region (Sheeler and Bianchi 662-663). The secretion of interleukin 1 and interleukin 2 is seen in the first step of the humoral immune response. Interleukin 1 influences T cell and B cell differentiation, whereas interleukin 2 helps to maintain "clonal growth of activated T cells" (Theofilopoulus,

Prudhomme, and Dixon 203).

In SLE, the production of both interleukin 1 and interleukin 2 is decreased. It is possible that IL-1 inhibitory factors decrease interleukin 1 activity. Recall that IL-1 inhibitors can be produced by monocytes, which can be stimulated by immune complexes. There is also a decrease in the production of interleukin 2 by SLE lymphocytes. This was found in patients with active SLE, as well as in patients with inactive SLE, thus making this defect different from other SLE T cell defects (Wallace and Dubois 204). Although IL-2 inhibitors are present in the serum, their levels seem to be decreased. Another possible cause of decreased interleukin 2 production could be a problem with T4+ lymphocytes (Theofilopoulus, Prudhomme, and Dixon 204). However, the decreased interleukin 2 production exists in SLE patients with and without normal percentages of T4+ lymphocytes. Furthermore, it has been found that the T4+ lymphocytes' capacity to produce interleukin 2 is intact. The

actual cause of decreased IL-2 production seems to be the "spontaneously activated T8+ lymphocytes." When T8+ lymphocytes are removed, IL-2 production in active and in inactive SLE is restored. The readdition of T8+ cells inhibits production of interleukin 2 again. Thus, it is believed that interleukin 2 production is inhibited by T8+lymphocytes (Wallace and Dubois 204).

In the immune response, interleukin 2 stimulates the production of interferon, which is another type of lymphokine (Blau and Schultz 69). Because interleukin 2 is very important in the humoral immune response, the effects of interferon on antibody production are important also (Wallace and Dubois 204). As mentioned earlier, interferon is also necessary for the proliferation of natural killer cells (Sheeler and Bianchi 669). In SLE patients, the levels of interferon are elevated even though interleukin 2 levels are decreased. This seeming paradox has not yet been explained (Blau and Schultz 69).

It is known that there are three classes of interferon: alpha, beta, and gamma. Alpha interferon is acid stable and is capable of increasing natural killer cell activity and activating nonspecific suppressor cells. Gamma interferon is acid labile and is able to inhibit proliferation of lymphocytes and enhance maturation of B cells. SLE patients, however, have increased levels of an "acid labile alpha interferon." No one knows the biological effects of this unusual interferon (Wallace and Dubois 204).

B Cell Hyperactivity

All of the factors described above contribute to the abnormal immune response, which seems to be characterized by the hyperactivity of B cells. B cell hyperactivity is most likely caused by several mechanisms that work together and produce excess antibodies. In murine SLE-like diseases, a primary B cell defect exists at the level of the stem cell. In addition, hypergammaglobulinemia and autoantibodies provide evidence for an inherited primary B cell defect

because they are found in SLE patients, as well as in family members and identical twins who are not afflicted by the disease (Wallace and Dubois 208).

SLE B cells do not act alone, rather they are regulated by other cells. Recall that in SLE, B-cell growth factor levels are increased, and that they "may be produced by T helper cells or certain CR3+ non-T cell subsets." Lymphokines can stimulate the CR3+ lymphocytes without an antigen present. Because of this possibility, the increased amounts of alpha interferon could stimulate SLE B cells to produce immunoglobulin or to maintain production of B-cell growth factors. In addition to this, it is known that soluble factors that increase B cell activity can be secreted by the B cells themselves (Wallace and Dubois 208).

Another aspect of B cell activity to be considered is the relationship between B cell hyperactivity and decreased interleukin 1 and interleukin 2 production. Recall that production of interleukin 2 is decreased in patients with

active and inactive SLE. Because of this, it is likely that the decrease in interleukin 2 production is a "primary defect that may be related to impaired generation of suppressor cell function." It is possible that the lymphocytes that produce B cell growth factor require less IL-2 than what is needed for the activation of suppressor cells. If this is true, "then correction of the IL-2 defect might result in the activation of suppressor cells capable of inhibiting the production of B cell growth factors" (Wallace and Dubois 208).

The suppressor cell defect, however, could only be corrected if the appropriate subsets are present for suppressor cell activation. Antilymphocyte antibodies that are present in SLE can deplete the T4+ suppressor inducer cells, and inadequate suppression would result even with normal levels of interleukin 2. Because patients with inactive SLE almost always have normal amounts of T-cell subsets and low levels of antilymphocyte antibodies, B cell hyperactivity cannot always be attributed to decreased

numbers of suppressor inducer cells (Wallace and Dubois 209).

It seems that researchers have a great deal of information about the abnormalities of the SLE immune response. They know that the numbers of lymphocytes are decreased, some of the ways that B and T lymphocytes are abnormal, the problems with the natural killer cells and monocytes, and the abnormal functions of the lymphokines. They are also quite sure that, in some way, all of these problems contribute to B cell hyperactivity, which seems to play a great role in SLE. Despite all of this knowledge, however, they still cannot clarify the exact mechanisms for B cell hyperactivity and the abnormal immune response. This area, then, is under continuous research and study in hopes of someday discovering exactly how SLE affects the immune system.

AUTOANTIBODIES IN SLE

By looking at the normal immune response and the

abnormal SLE immune response, one can only begin to comprehend the complexity of a multi-system autoimmune disease like SLE. One manifestation of this disease is the presence of autoantibodies in SLE serum. The most significant of the autoantibodies are those that are directed indiscriminately against nuclear antigens, the antinuclear antibodies (Blau and Schultz 20). As one of the criteria for the American Rheumatism Association's classification of SLE, the presence of antinuclear antibodies (ANA) obviously plays a great role in the development and in the detection of the disease (McCarty, Valencia, and Fritzler 8).

Immunofluorescence

Tests for antinuclear antibodies have been positive in more than 90% of SLE patients, and in less than 5% of other people. The only exception to these results is in patients with rheumatoid arthritis, two-thirds of which may have ANA, but at lower levels than SLE patients (Blau and Schultz 20). Antinuclear antibodies are detected by

immunofluorescence. In this technique, patient samples and an antigen substrate are incubated together to allow the specific binding of cell nuclei and autoantibodies. An antigen-antibody complex is formed if ANA are present. Antibodies that are not specifically bound are washed off. An "anti-human antibody reagent conjugated with fluorescein" is then incubated with the substrate (McCarty, Valencia, and Fritzler 42). After being washed a second time, a fluorescent microscope is used to view the slides (Wallace and Dubois 229). When positive results are obtained, a stable three-part complex exists where the fluorescent antibody is bound to the human antinuclear antibody that is bound to the nuclear antigen. This complex will be a fluorescent apple-green. If the results are negative for antinuclear antibodies, there will be no fluorescence (McCarty, Valencia, and Fritzler 42).

Once positive results for the immunofluorescence-antinuclear antibody test (IFA-ANA) are obtained, the

resulting pattern can help determine the type of antinuclear antibody present. There are three types of ANA patterns that may indicate the presence of SLE. These patterns are most easily seen in cells undergoing mitosis, which greatly increases the ability to determine the antigen specificity of these autoantibodies. Before cell division, most nuclear antigens are uniformly distributed throughout the nucleus. However, the nuclear antigens are redistributed when the chromosomes condense and the nuclear membrane is fragmented. Only antigens such as DNA and histone that are associated with chromosomes are able to fluoresce. During cell division, the other nuclear antigens, such as Sm and RNP, are redistributed outside of the chromosome region (McCarty, Valencia, and Fritzler 65).

In the homogenous pattern, the entire nucleus is smoothly stained. Occasionally, the nucleoli will not appear to be stained. In metaphase, the chromosome region is definitely positive. A homogenous pattern may indicate the

presence of the following nuclear antigens: deoxyribonucleoprotein (DNP), double-stranded DNA, and histone (McCarty, Valencia, and Fritzler 66).

In the peripheral pattern, the smooth staining is located basically around the outer region of the nucleus. Weaker staining often occurs toward the center of the nucleus. The chromosome region is positive. This pattern may be described as shaggy or membranous. The nuclear antigens that may be present are double-stranded DNA, single-stranded DNA, DNP, and histone. If staining of the chromosome region does not occur, it is improbable that anti-DNA, anti-histone, or anti-DNP are present (McCarty, Valencia, and Fritzler 66).

In the speckled pattern, the nucleus appears to have a fine, or grainy, stain. Usually, the nucleolar region is not stained. The chromosome region does not stain, either. The area outside the chromosome region stains with a varying intensity. The following antigens may be present: Smith

antigen (Sm), nuclear ribonucleoprotein (nRNP), Sjogren's syndrome A antigen (SS-A), or scleroderma 70 antigen (Scl-70) (McCarty, Valencia, and Fritzler 66).

By using the technique of immunofluorescence and looking at the patterns it produces, autoantibodies can be detected in SLE serum. These autoantibodies may be antibodies to DNA, antibodies to deoxyribonucleoprotein, antibodies to histone, or antibodies to nonhistone nuclear antigens.

Antibodies to DNA

High titers of anti-DNA antibodies do not necessarily make the diagnosis of SLE correct, but they strongly suggest the presence of that autoimmune disease. Anti-DNA antibodies can be categorized according to which type of DNA they react with. They may react with sites on double-stranded DNA, with sites on single-stranded DNA, or with sites on both double-stranded DNA and single-stranded DNA (Glass and Schur 544).

Anti-double-stranded DNA antibodies are uniquely specific to SLE (Blau and Schultz 22). They are of the IgG or IgM class and are targeted to the carbohydrate phosphate backbone of the DNA (Glass and Schur 545). The presence of these antibodies is greatly increased during active SLE and active nephritis. By measuring a patient's antibodies to double-stranded DNA, their pattern of disease activity can be followed (Wallace and Dubois 231).

Ninety percent of SLE patients have antibodies to single-stranded DNA (Blau and Schultz 22). Their presence is not always indicative of SLE, however, because they are frequently seen in other systemic rheumatic diseases (Wallace and Dubois 231). Like double-stranded DNA antibodies, anti-single-stranded DNA is present in high titer in patients with active nephritis (Glass and Schur 545).

The final class of anti-DNA antibodies reacts with both single-stranded DNA and double-stranded DNA. Although they probably recognize the carbohydrate-phosphate

backbone of DNA, a single strand of the backbone would not be sufficient to make the antibodies antigenic for both single-stranded DNA and double-stranded DNA. One possibility for the antigenic site is that the single-stranded DNA may form a helical structure by folding back on itself. An antigenic determinant would be created that could react to antibodies specific for both single-stranded DNA and double-stranded DNA (Wallace and Dubois 230).

Antibodies to Deoxyribonucleoprotein

Deoxyribonucleoprotein (DNP) is nuclear material made up primarily of DNA-histone complexes (McCarty, Valencia, and Fritzler 31). Antibodies to DNP are indirectly responsible for the LE cell (lupus erythematosus cell) phenomenon (Wallace and Dubois 232). Basically, the anti-DNP antibodies react and complex with nuclei from leukocytes that have been disrupted. Viable leukocytes then phagocytose the immune complexes and form the LE cell (Glass and Schur 541). Approximately 70% of SLE patients have the LE cell

and the antibody to DNP present in their serum. Since they can be found in other rheumatic diseases, however, the LE cell and anti-DNP antibody are not specific for SLE (Wallace and Dubois 232).

Antibodies to Histone

Histones are a group of basic nuclear proteins that contain high ratios of the amino acids arginine and lysine. Antibodies to histones can react with all of the histone classes: "H1, H2A, H2B, H3, and H4." H2A and H2B are able to complex with each other. This complex, too, is recognized by specific autoantibodies (Wallace and Dubois 232).

There are differing reports on the percentages of idiopathic SLE patients with antibodies to histone. Wallace and Dubois report that up to 86% of patients with idiopathic SLE have antihistone antibodies (234), while McCarty, Valencia, and Fritzler report that only 30% do (34). Both report that antibodies to histone are present in 90% or more

of the patients with drug-induced lupus erythematosus (Wallace and Dubois 234; McCarty, Valencia, and Fritzler 35).

Histones express a homogenous immunofluorescence pattern (McCarty, Valencia, and Fritzler 35). It is difficult, however, to be certain that the pattern represents histone antigen because it is so similar to the anti-DNA pattern. For this reason, an enzyme-linked immunosorbent assay and a radioimmunoassay have been developed to detect the presence of antihistone antibodies (Wallace and Dubois 234).

Antibodies to Nonhistone Nuclear Antigens

The final class of antinuclear antibodies found in SLE is reactive with nonhistone nuclear proteins. In IFA-ANA tests, these nonhistone proteins express the speckled pattern. This pattern may be due to different antigenic specificities. Because it is "one of the least specific ANA patterns," the antigen is further detected by immunodiffusion (ID), passive hemagglutination (PHA), or counterimmunoelectrophoresis

(CIE). There are six types of nonhistone nuclear proteins that may be present in SLE: Smith antigen, nuclear ribonucleoprotein, Sjogren's syndrome A antigen and B antigen, MA-1 antigen, and proliferating cell nuclear antigen (McCarty, Valencia, and Fritzler 35).

The antibody to the Smith antigen (anti-Sm) was the first nonhistone antigen discovered (Wallace and Dubois 235). It was described using an agarose gel precipitin system. The Smith antigen shows resistance to treatment with RNase and DNase, but is inactivated by treatment with periodate and trypsin. Once the immunofluorescent speckled pattern has been detected, the presence of Smith antigen can be determined by ID against calf thymus extract or rabbit thymus nuclear extract, by PHA, or by CIE (McCarty, Valencia, and Fritzler 35). If the Smith antigen is detected, the patient is then known to have SLE because anti-Sm antibody is totally specific for SLE (Blau and Schultz 22). Moreover, its significance is proven because it is included in

the antinuclear antibody criteria for SLE even though it is present in only 30% of SLE patients (Wallace and Dubois 235).

Another nonhistone nuclear antigen is nuclear ribonucleoprotein (nRNP). Antibodies to nRNP are present in highest titer in mixed connective tissue disease, which mimics scleroderma, SLE, and dermatomyositis. There are, however, high titers of antibodies to nuclear ribonucleoprotein in SLE (Wallace and Dubois 236). Obviously, unlike the anti-Sm antibody, anti-nRNP is not specific for SLE. However, antibody to nRNP is more common in SLE patients than the anti-Sm antibody is. There appears to be a linkage between the responses of antibodies to nRNP and to Smith antigen. Although the antigenic determinants of each are clearly independent, concurrent immune responses to these antigens occur much more frequently than is predicted by chance. Because of this, anti-nRNP and anti-Sm are present together more often than anti-

Sm alone (Schur 56). It has now been found that the Sm antigen and the nRNP antigen associate in extractable nuclear antigen (ENA) complexes (Wallace and Dubois 236).

There are two types of antinuclear antibodies that occur primarily in patients with Sjogren's syndrome, and in a significant percentage of SLE patients. The two types of antibodies are known as anti-SS-A and anti-SS-B because they were first seen in patients with Sjogren's syndrome. When the SS-A antigen and the SS-B antigen were discovered, they were considered to be nuclear antigens. Two other antigens known as Ro and La had been discovered and were considered cytoplasmic antigens. It turns out that different researchers were describing the same antigens and naming them differently. Now the antibodies to these antigens are known as anti-SS-A/Ro and anti-SS-B/La antibodies. Because these antibodies are made of RNA-protein complexes, they can be found in the nucleus and in the cytoplasm. RNA is made in the nucleus, but some of it

can be found in the cytoplasm. Therefore, the researchers may have been looking at the antibodies during different stages of the cell cycle and seeing what were thought to be different antigens (Wallace and Dubois 237).

Anti-SS-A/Ro antibodies can be found in 30 to 40% of SLE patients, and in up to 70% of Sjogren's syndrome patients. There are several clinical associations between features of SLE and the presence of anti-SS-A/Ro antibodies. One example is the presence of "extensive photosensitive dermatitis" (Wallace and Dubois 238). Another example is the association of anti-SS-A/Ro antibodies with neonatal lupus. Often these children have rashes and complete heart block (McCarty, Valencia, and Fritzler 36). In addition, the titers of anti-SS-A/Ro change with disease activity and with levels of antibody to double-stranded DNA, thus making it possible to use this antibody to quantitate SLE activity (Wallace and Dubois 238).

Anti-SS-B/La antibodies are seen in fewer SLE patients

than are antibodies to SS-A/Ro. Antibody to SS-B/La is found in approximately 15% of SLE patients, and in 45 to 60% of Sjogren's syndrome patients (Schur 58). There are no clinical manifestations of SLE directly associated with the presence of antibody to SS-B/La (Wallace and Dubois 238).

Antibodies to SS-A/Ro and antibodies to SS-B/La react with RNA-protein complexes. The small RNAs are made up primarily of RNA polymerase III transcripts. It has been found that the SS-B/La antigen assists in "the maturation of RNA polymerase III transcripts." Also, the SS-B/La protein is known to bind EBV-associated RNA and adenovirus-associated RNA. It is possible these viruses play a part in a disease where the antibody to SS-B/La is present. This is only a possibility, however, since little is understood about the soluble nuclear antigens (Wallace and Dubois 239).

Proliferating cell nuclear antigen (PCNA) is found in greatest amounts in the nuclei of proliferating cells (McCarty, Valencia, and Fritzler 37). The antibody to PCNA does not

react with interphase cells that are not dividing, rather it reacts with rapidly proliferating cells or mitogen-stimulated cells. Proliferating cell nuclear antigen can be found in different cell types such as activated B and T lymphocytes, germline cells, and epithelial cells. After being stimulated by concanavalin A, PCNA can be seen in the nucleolus. Then it appears to move to the nucleoplasm and disappear in the "blast-transformed lymphocyte." Since PCNA is reactive only with dividing cells, it is immunologically distinct from other nuclear antigens such as DNA, Sm, nRNP, SS-A/Ro, and SS-B/La. In addition, it seems that PCNA is highly, or totally, specific for SLE (Wallace and Dubois 239). Because it is present in less than 10% of SLE patients, however, it is very hard to draw complete conclusions about this "unique nuclear protein" (McCarty, Valencia, and Fritzler 37-38).

MA-1 is another nonhistone nuclear antigen. The antibody to MA-1 appears to be distinct in its immunofluorescent pattern. The beaded peripheral pattern is

unlike the patterns seen for other nuclear antigens such as nRNP, Sm, SS-A/Ro, or SS-B/La (McCarty, Valencia, and Fritzler 37). Using immunodiffusion in one study, twelve of sixty-six SLE patients (approximately 18%) had antibodies to MA-1 antigen. Furthermore, in another study, this antibody was not seen in 554 patients with other systemic rheumatic diseases and normal individuals. Therefore, there appears to be a high specificity of anti-MA-1 antibodies for SLE. The patients that have antibodies to MA-1 present represent a subset of SLE because of the specific clinical manifestations associated with the MA-1 antigen. These features are some of the most severe implications of SLE: "recalcitrant skin lesions, hypocomplementemia, severe renal disease, and neurologic abnormalities." In the study of SLE patients with anti-MA-1 antibodies, the disease had taken a very progressive course. Three patients had MA-1 antigen circulating in their bodies just before the onset of nephritis. This association between the MA-1 antigen and nephritis

suggests that "MA antigen-antibody complexes may be present in immune-complex mediated tissue injury" (Wallace and Dubois 239).

The many types of antinuclear antibodies described above play an important role in the diagnosis of SLE and in the tracking of disease activity. Because they are present in 99% of SLE patients and are easily detected by immunofluorescence, antinuclear antibodies can be observed and recorded with ease (Wallace and Dubois 227). Then, using the results, the type and necessity of treatment can be evaluated.

CONCLUSION

Treating lupus is as varied as its many manifestations and symptoms. No specific treatment is necessary for those patients who are asymptomatic except for the presence of a few antinuclear antibodies or LE cells. Bed rest is prescribed for those who are experiencing active disease. When mild arthritis is the main complaint, bed rest and "nonsteroidal

anti-inflammatory agents" are prescribed. If a patient is one of those 10% who experience a severe case of SLE with neurological or renal involvement, corticosteroids are prescribed (Wallace and Dubois 502).

Outside of these medical recommendations and prescriptions, lupus patients must simply learn to live with the manifestations of their illness. Patients must avoid the sun and use protective sunscreens. They must get adequate rest, especially during the early stages of remission, to avoid triggering disease activity. SLE patients, however, must also get adequate amounts of exercise, especially those that strengthen muscles without stressing joints. Physical therapists can instruct patients in the proper use of exercise. Finally, patients should follow a well-balanced diet (Hales 60). These recommendations hardly seem life-altering, however, because they should be a part of the lifestyle of a healthy individual, as well.

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